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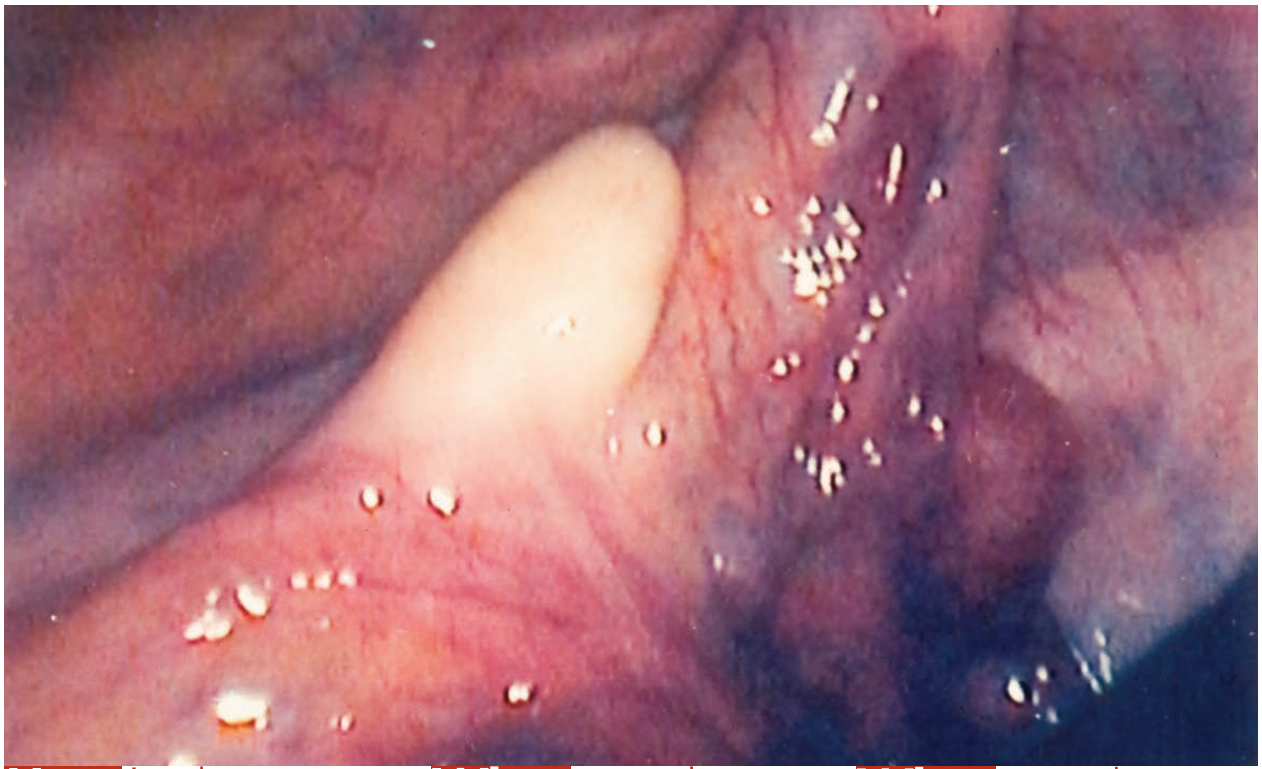


FIGURE 1
Streak ovary in a patient with Turner's syndrome seen during laparoscopy

How is the condition diagnosed?

PREMATURE MENOPAUSE IS A LIFE-CHANGING MEDICAL CONDITION. IT CAN MEAN THE END OF fertility. The condition affects 1% of women under the age of 40, 1 in 1,000 under the age of 30 and 1 in 10,000 under the age of 20. In the UK, each year, 110,000 women will experience premature menopause between the ages of 12 and 40.[3]

In utero, as many as 6-7 million oogonia are present by 16-20 weeks. This represents the peak and from this point onwards, the numbers of oogonia start to decline. At birth, the ovaries contain 1-2 million oocytes all arrested in the first stage of meiosis. At the onset of puberty, the oocytes have reduced to 300,000 and over the next 35-40 years, these will be depleted further with only a few hundred remaining by the menopause which usually occurs around the age of 51. Smokers are likely to reach the menopause approximately 18 months earlier. There is no correlation between age of menarche, race, parity and height with age at menopause.

Common menopausal symptoms are listed in table 1, p22. Long-term deprivation of oestrogen can result in serious health problems such as osteoporosis and cardiovascular disease.

DIAGNOSIS

The first steps to diagnosis involve:

- History and examination
- Urine pregnancy test
- Progestagen challenge test
- Serum tests: FSH, LH, TSH, prolactin, oestradiol

What are the common causes?

What are the potential complications?

Most women will present with irregular periods or no periods at all with or without climacteric symptoms. Around 10% of women present with primary amenorrhoea. A careful history and examination are required. It is important to ask specifically about previous chemotherapy or radiotherapy and to look for signs of androgen excess e.g. polycystic ovarian syndrome, adrenal problems e.g. galactorrhoea (hyperprolactinaemia) and thyroid goitres (see table 2, p22).

Differential diagnoses are listed in table 3, p22.

INITIAL INVESTIGATIONS

It is appropriate at this stage to perform a progestagen challenge test, once pregnancy has been excluded. This can be carried out in primary care. We prescribe norethisterone 5mg »

Table 1

Common menopausal symptoms

- Irregular periods
- Infertility
- Hot flushes and night sweats
- Insomnia/disrupted sleep
- Palpitations
- Weight gain (especially around waist and abdomen)
- Skin and hair changes (dryness, thinning)
- Headaches
- Breast tenderness
- Mood swings and irritability
- Anxiety/panic attacks
- Loss of self-esteem
- Lowered libido
- Difficulty concentrating and memory lapses
- Fatigue/low energy levels
- Vaginal dryness and UTIs
- Depression

Table 2

Common causes of premature menopause

- Idiopathic
- Radiotherapy or chemotherapy
- Surgical
- Chromosomal (46 X0, 46XY) or genetic (FMR1 premutation)
- Autoimmune conditions (hyper- or hypothyroidism, adrenal insufficiency, diabetes)

tds po for ten days or alternatively medroxyprogesterone acetate 10mg daily for ten days. A withdrawal bleed within a few days of stopping the norethisterone indicates the presence of oestrogen and bleeding more than a few drops is considered a positive withdrawal bleed. The absence of a bleed indicates low levels of oestrogen, therefore putting the woman at risk of cardiovascular disease and osteoporosis.

The presence of a bleed should not exclude premature menopause as part of the differential diagnosis. Up to 50% of women with this condition can have a withdrawal bleed, as there can be varying and unpredictable ovarian function remaining. Because of this it is more accurate to describe the condition as 'premature ovarian dysfunction or insufficiency'.[1] Around 5-10% of women with this diagnosis have gone on to have a successful pregnancy.

The progestagen challenge test should not be used alone, but in conjunction with FSH, LH and oestradiol.

Table 3

Differential diagnoses

Hypothalamic amenorrhoea	Low oestrogen caused by an underactive hypothalamus or pituitary e.g. due to extreme weight loss (reduced calorie intake or excessive exercise), or emotional stress
Hyperprolactinaemia	This is usually caused by excess secretion of prolactin from the pituitary gland. Other rare causes include ectopic secretion associated with pituitary tissue in the pharynx, bronchogenic carcinoma, renal cell carcinoma, gonadoblastoma and amenorrhoea, and hyperprolactinaemia due to a prolactinoma in the wall of an ovarian dermoid cyst
Polycystic ovarian syndrome	It is important to note that PCOS is not associated with low oestrogen
Primary ovarian failure	High levels of gonadotrophins because of a lack of ovarian response (depleted stores or dysfunction of the ovary)

A positive withdrawal bleed in response to progestagens, the absence of galactorrhoea and a normal prolactin level together effectively rule out the presence of a significant pituitary tumour.

The lack of a withdrawal bleed indicates that either preliminary oestrogen proliferation has not occurred or that there is an outflow tract obstruction. A course of oestrogen followed by progestagen will clarify this situation. We prescribe 21 days of oestrogen (conjugated oestrogens 1.25mg daily) with the addition of medroxyprogesterone acetate 10mg daily for the last ten days. If there is a withdrawal bleed, it can be assumed that the outflow tract has normal functional abilities, if properly stimulated by oestrogen.

The blood tests are carried out to determine if the lack of oestrogen is due to a fault in the ovary or in the hypothalamic-pituitary axis.

A high level of FSH indicates an underactive ovary (see table 4, below). FSH levels above 30 IU/L are an indicator that the ovaries are failing and the menopause is approaching or has occurred. It should be remembered that FSH levels fluctuate during the month and from one month to the next, so a minimum of two measurements should be made at least four to six weeks apart.

The presence of a high LH and FSH is a very reliable indicator of ovarian failure.

'The presence of a high LH and FSH is a very reliable indicator of ovarian failure'

FURTHER INVESTIGATION

Once premature menopause has been diagnosed the following investigations should be carried out:

- chromosome analysis and genetic studies (FMR1 if strong family history)
- autoantibody screen, FBC, calcium, cortisol
- transvaginal ultrasound scan: to identify follicles (pre-antral count)
- DEXA scan for baseline bone density

The most common genetic abnormalities are 45, X and 47, XXY and mosaicism. The presence of mosaicism with a Y chromosome requires excision of the gonads because any testicular component within the gonad carries with it a significant chance of malignant tumour formation. Short stature is linked with Turner's syndrome. If a »

Table 4

Serum FSH and LH levels

	Serum FSH	Serum LH
Normal adult female	5-30 IU/L with the ovulatory midcycle peak about two times the base level	5-20 IU/L with the ovulatory midcycle peak about three times the base level
Hypogonadotrophic state	< 5 IU/L	< 5 IU/L
Hypergonadotrophic state	> 30 IU/L	> 40 IU/L

key points

SELECTED BY

Dr Peter Saul
GP, Wrexham and associate GP Dean for North Wales

Premature menopause affects 1% of women under the age of 40, the usual age of the menopause is 51. Most women will present with irregular periods or no periods at all with or without climacteric symptoms. Around 10% of women present with primary amenorrhoea. A careful history and examination are required. It is important to ask specifically about previous chemotherapy or radiotherapy and to look for signs of androgen excess e.g. polycystic ovarian syndrome, adrenal problems e.g. galactorrhoea and thyroid goitres.

Once pregnancy has been excluded, a progestagen challenge test can be performed in primary care. Norethisterone 5 mg tds po for ten days or alternatively medroxyprogesterone acetate 10 mg daily for ten days is prescribed. A withdrawal bleed within a few days of stopping the norethisterone indicates the presence of oestrogen and bleeding more than a few drops is considered a positive withdrawal bleed. The absence of a bleed indicates low levels of oestrogen, putting the woman at risk of cardiovascular disease and osteoporosis. FSH levels above 30 IU/l are an indicator that the ovaries are failing and the menopause is approaching or has occurred. It should be remembered that FSH levels fluctuate during the month and from one month to the next, so a minimum of two measurements should be made at least four to six weeks apart.

The presence of a bleed should not exclude premature menopause as part of the differential diagnosis as there can be varying and unpredictable ovarian function remaining.

The progestagen challenge test should not be used alone, but in conjunction with FSH, LH and oestradiol. A positive withdrawal bleed in response to progestagens, the absence of galactorrhoea and a normal prolactin level together effectively rule out the presence of a significant pituitary tumour. The lack of a withdrawal bleed indicates that either preliminary oestrogen proliferation has not occurred or that there is an outflow tract obstruction. A course of oestrogen followed by progestagen will clarify this situation.

There is no treatment for premature menopause. Women desiring pregnancy should be referred to a fertility clinic and discussion of egg donation. Women not wishing to become pregnant should be prescribed HRT until the age of 50. The aim of HRT is to control symptoms of oestrogen deficiency and reduce the risks of osteoporosis and CVD. HRT does not have a contraceptive effect, for women requiring contraception, the combined oral contraceptive pill is an alternative to HRT. It should not be used as first-line management as it provides more steroid hormone than is needed for natural replacement.

chromosomal abnormality is detected, it is important to discuss testing of first-degree relatives.

MANAGEMENT OPTIONS

There is no treatment for premature menopause. Management should ideally involve a multidisciplinary team covering:

- emotional health
- physical wellbeing
- bone protection
- cardiovascular protection
- family planning
- HRT

FERTILITY

A diagnosis of premature menopause can be very upsetting for women particularly the loss of fertility. It is vital to adopt a sensitive approach when giving the diagnosis and to allow time for the patient to ask questions. There are also websites and support groups that patients may find helpful (see useful information box, p26).

Women desiring pregnancy should be referred to a fertility clinic and discussion of egg donation.

It may be appropriate for GPs to manage premature menopause with HRT if the woman has completed her family. Daughters of these women may also experience a premature menopause and it may be appropriate to investigate further on their behalf. Discussion with a geneticist is recommended, particularly if there is more than one first-degree relative diagnosed with premature menopause, as there is evidence suggesting a genetic link (see table 2, p22). The genetics are beyond the scope of this article.

Women not wishing pregnancy should be prescribed HRT until the age of 50. The aim of HRT is to control symptoms of oestrogen deficiency and reduce the risks of osteoporosis, cardiovascular disease and possibly Alzheimer's disease.[4]

For many women taking HRT, the increased risk of breast cancer is a cause for great concern. All the published research so far has been on women over 50. It is thought that under this age the risk with HRT is similar to what it would have been if the ovaries had not failed prematurely. There is, however, no study to date directly investigating the risk of breast cancer with the use of HRT in women with premature menopause.[3]

The risk of developing heart disease for women who go through the menopause before 35 is two to three times that of women who do not. This risk is increased further if the ovaries have been surgically removed. However, the risk of suffering an ischaemic event seems to be reduced in women taking oestrogen therapy compared with non-users.[5,6] Therefore, HRT is prescribed as a preventative measure for women who have had a premature menopause. It is likely that HRT will help delay the onset of heart disease, although the extent of this benefit is not yet clear.[3]

CONTRACEPTION

HRT does not have a contraceptive effect. Rare cases of pregnancy have been reported in women presenting with secondary amenorrhoea and elevated gonadotrophins who several months later have resumed normal periods. Therefore it is important to enquire about whether the woman wishes to become pregnant.

In women requiring contraception, the combined oral contraceptive pill (COCP) is an alternative to HRT. It should not be used as first-line management as it provides more steroid hormone than is needed for natural replacement.[4] The COCP can be continued until the age of 50 in fit and well, non-smoking women.

HRT may be combined with alternative contraception, such as the IUS. As a practical point, women with premature menopause may require a higher dose of oestrogen than postmenopausal women and dose should be titrated against symptoms.

DIET AND EXERCISE

Lifestyle factors should be discussed to optimise general health. The diet should contain adequate amounts of vitamins C, K and B_6, copper, zinc, manganese, glucosamine, calcium and magnesium. Calcium, whether in the form of low-fat dairy products, dark green leafy vegetables or nuts e.g. almonds, is vitally important for bones. Current government recommendations are that perimenopausal and postmenopausal women should have a daily calcium intake of 1,500mg per day (1 pint of semi-skimmed milk contains 750mg).

Vitamin D helps with absorption of calcium and so it is vital either to add a vitamin D supplement or make sure there is adequate dietary intake. It is found in oily fish, fish liver oils and fortified margarines. A total of 15 minutes of sunshine is all that is »

needed to obtain the day's entire vitamin D requirement.

Weight-bearing exercise (e.g. light weights or jogging) is another key part in prevention of osteoporosis. Cycling is very good cardiovascular exercise, but less good for bone health.

The ovaries also produce testosterone and a woman's levels drop by 20% after a natural menopause and by 50% after a surgical menopause. It is thought that low testosterone levels result in poor libido and lack of energy. Testosterone replacement patches have been licensed for low libido following surgical removal of the ovaries and could be considered in women with surgical premature menopause.

CONCLUSION

Amenorrhoea has many causes and needs investigation. It is important to make the diagnosis of premature menopause to reduce the long-term consequences, notably osteoporosis. Investigations should begin in general practice with a progestagen challenge and serum FSH, LH and oestradiol. If pregnancy is desired, the patient should be referred to a fertility clinic for further investigation, advice and treatment.

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Useful information

The following organisations provide advice and support for patients with premature menopause.

www.daisynetwork.org.uk

www.pofsupport.org

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If you would like to comment on this article or share your experiences with other readers, write to:

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